High Density Lipoproteins: Is There a Comeback as a Therapeutic Target?

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Contents

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Abstract

Low plasma levels of High Density Lipoprotein (HDL) cholesterol (HDL-C) are associated with increased risks of atherosclerotic cardiovascular disease (ASCVD). In cell culture and animal models, HDL particles exert multiple potentially anti-atherogenic effects. However, drugs increasing HDL-C have failed to prevent cardiovascular endpoints. Mendelian Randomization studies neither found any genetic causality for the associations of HDL-C levels with differences in cardiovascular risk. Therefore, the causal role and, hence, utility as a therapeutic target of HDL has been questioned. However, the biomarker "HDL-C" as well as the interpretation of previous data has several important limitations: First, the inverse relationship of HDL-C with risk of ASCVD is neither linear nor continuous. Hence, neither the-higher-the-better strategies of previous drug developments nor previous linear cause-effect relationships assuming Mendelian randomization approaches appear appropriate. Second, most of the drugs previously tested do not target HDL metabolism specifically so that the futile trials question the clinical utility of the investigated drugs rather than the causal role of HDL in ASCVD. Third, the cholesterol of HDL measured as HDL-C neither exerts nor reports any HDL function. Comprehensive knowledge of structure-function-disease relationships of HDL particles and associated molecules will be a pre-requisite, to test them for their physiological and pathogenic relevance and exploit them for the diagnostic and therapeutic management of individuals at HDL-associated risk of ASCVD but also other diseases, for example diabetes, chronic kidney disease, infections, autoimmune and neurodegenerative diseases.

Keywords

Apolipoprotein A-I · CETP · Cholesterol efflux · Fibrate · HDL mimetic · High density lipoproteins · Nicotinic acid

1 Introduction

Low plasma levels of high density lipoprotein (HDL) cholesterol (HDL-C) are associated with increased risks of atherosclerotic cardiovascular diseases (ASCVD), notably coronary heart disease (CHD) (Emerging Risk Factors Collaboration 2009; Madsen et al. 2021). HDL particles exert a broad spectrum of biological activities many of which are considered as anti-atherogenic, for example mediation of cholesterol efflux from macrophage foam cells and reverse transport of cholesterol to the liver, promotion of endothelial integrity and function, inhibition of inflammation by suppression of myelopoiesis and transmigration of leukocytes through the endothelium as well as macrophage activation, inhibition of lipid oxidation as well as inactivation of oxidized lipids (Fig. 1) (Von Eckardstein and Kardassis 2015; Robert et al. 2021; Rohatgi et al. 2021). Furthermore, atherosclerosis could be

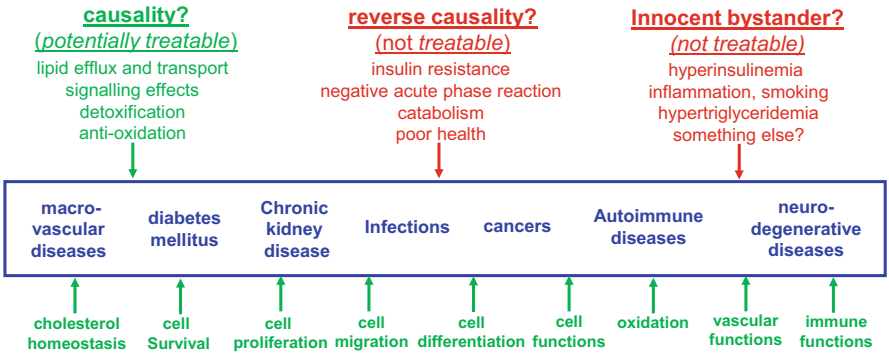

Fig. 1 Possible pathophysiological relationships of low HDL cholesterol with its associated diseases (modified from Von Eckardstein and Kardassis 2015)

decreased or even reverted in several animal models by transgenic over-expression or exogenous application of apolipoprotein (apoA-I), i.e. the most abundant protein of HDL (Hoekstra and Van Eck 2015; Lee-Rueckert et al. 2016). However, in humans, drugs increasing HDL-C such as fibrates, nicotinic acid (niacin), or inhibitors of cholesteryl ester transfer protein (CETP) have failed to prevent fatal or non-fatal cardiovascular endpoints (Keene et al. 2014; Riaz et al. 2019). Infusions of reconstituted HDL (rHDL) did not lead to regression of atherosclerosis in coronary or carotid arteries (He et al. 2021). Moreover, in several inborn errors of human HDL metabolism and genetic mouse models with altered HDL metabolism, low or high HDL-C levels were not always associated with the differences in cardiovascular risk and atherosclerotic plaque load, respectively, that were expected from epidemiology (Hoekstra and Van Eck 2015; Lee-Rueckert et al. 2016; Zanoni and von Eckardstein 2020). For example, the loss of scavenger receptor B1 (SR-BI) function aggravates the risk of ASCVD events in human carriers of SCARB1 mutations and promotes atherosclerosis in Scarb1 knock-out mice despite increasing HDL-C levels (Hoekstra and Van Eck 2015; Lee-Rueckert et al. 2016; Zanoni et al. 2016). Because of these ambiguous data, the causal role of HDL in the pathogenesis of atherosclerosis as well as the suitability of HDL-C as a therapeutic target is nowadays scrutinized if not doubted (Madsen et al. 2021; März et al. 2017). Both the previous euphoria and the current skepticism in the discussion of HDL's role in health and disease, specifically in ASCVD but also beyond, have been suffering from several misconceptions, which are described in the first part of this review. As the conclusion, several perspectives for the clinical exploitation of HDL are presented in the second part.

2 Possible Reasons for HDL-C's Clinical Futility

2.1 Lack of Causality

Mendelian randomization studies have been a successful tool to support the causality of LDL cholesterol (LDL-C) in atherosclerosis: Single nucleotide polymorphisms (SNPs) and rare genetic variants that are associated with lower or higher LDL-C levels are associated with lower and higher risk, respectively, of ASCVD events. The associations of genetically determined LDL-C with ASCVD risk are even stronger than the associations of measured LDL-C. This is because the genetic information includes both time and dosage of exposure to the harmful LDL-C whereas the measured LDL-C only records the dosage of the harm (Borén et al. 2020). Mendelian randomization studies also support causality of hypertriglyceridemia and elevated apoB levels as well as hypertension in the pathogenesis of ASCVD (Benn and Nordestgaard 2018). Conversely, this genetic strategy rather excluded genetic causality of HDL-C and apoA-I levels in the manifestation of ASCVD, at least after maximal adjustment for confounding lipid traits such as apoB and triglyceride levels (Richardson et al. 2020; Voight et al. 2012). However, it is important to note the limitations of Mendelian Randomization studies. With respect to HDL-C the most important limitation is the assumption of a continuous relationship between the risk factor and the clinical endpoint. This is true for the association of LDL-C or nonHDL-C with major cardiovascular events but not for HDL-C, where no difference in risk is observed among individuals with HDL-C levels above the 60th percentile (Emerging Risk Factors Collaboration 2009; Johannesen et al. 2020; Madsen et al. 2017; see Sect. 2.2).

HDL-C levels below the widely accepted risk thresholds of 1.0 mmol/L or 40 mg/dL are frequently confounded by other risk factors of ASCVD, notably hypertriglyceridemia, manifest diabetes mellitus type 2 (T2DM) or impaired fasting glucose, smoking, chronic inflammatory diseases (chronic obstructive lung disease, rheumatic diseases) or biomarkers of inflammation (e.g., elevated C-reactive protein), overweight or obesity (Fig. 1; Assmann et al. 1996; Damen et al. 2017). Due to the links of HDL metabolism with the metabolism of triglyceride-rich lipoproteins, it has been suggested that low HDL-C is an indirect long-term indicator of postprandial hypertriglyceridemia and hence exposure of atherogenic remnants like elevated glycated hemoglobin A1c is a long-term marker of disturbed glucose metabolism but a non-causal risk factor of glycation-induced organ damage (Langsted et al. 2020).

2.2 Epidemiology and Human Genetics Disprove "the Higher the Better" Concept

The association of HDL-C with risk of ASCVD events has been described for decades to be inverse. The resulting widespread reception of HDL-C as the "good cholesterol" led to the application of "the higher the better" strategies to both patient counselling and drug development. However, the meta-analysis of 68 population

studies with more than 300,000 participants and 2,785 incident myocardial infarctions by the Emerging Risk Factors Collaboration found the unadjusted risk of myocardial infarction gradually decreasing from the first decile to the eighth decile (i.e., until about 1.5 mmol/L or 58 mg/dL) but no significant changes at higher levels of HDL-C. After adjustment for possible confounders, statistically significant dose-dependent risk decreases happen within the lower six deciles until about 50 mg/dL (1.3 mmol/L) but not above this threshold (Emerging Risk Factors Collaboration 2009). Similar observations were made in more than 110,000 and 630,000 participants of the Copenhagen General Population (CGPS) and Copenhagen City Heart Studies (CCHS) and CANHEART studies (Madsen et al. 2017; Wijeysundera et al. 2017). In Denmark, the decreases in risk of cardiovascular events reached plateaus at 1.5 mmol/L in men and 2.0 mmol/L in women (Madsen et al. 2017). In Canada, below the reference interval ranging from 50 to 60 mg/dL, the incidence of ASCVD events increased with every decreasing 10 mg/dL interval of HDL-C. Above the threshold of 60 mg/dL, the ASCVD risks were overall significantly lower compared to the reference interval, but did not differ between the increasing 10 mg/dL strata, neither in men nor in women (Wijeysundera et al. 2017). Of note, the associations of HDL-C with total as well as disease-specific mortalities including cardiovascular mortality are even parabolic (U-shaped): Both in the Danish and Canadian studies, the inverse associations of HDL-C with total mortality reached their nadirs at 1.8–1.9 mmol/L (70–75 mg/dL) and 2.3–2.4 mmol/L (90–95 mg/dL) in men and women, respectively. Beyond these thresholds, the risk of dying became gradually higher with further increasing HDL-C levels (Ko et al. 2016; Madsen et al. 2017).

The discontinuous and even parabolic associations of HDL-C with cardiovascular morbidity and mortality, respectively, have been largely ignored both in the execution of Mendelian randomization studies and in the design of randomized controlled studies that aimed at the lowering of cardiovascular risk by increasing of HDL-C: both have been based on the assumption of continuous the-higher-the-better associations. The majority of the trials on fibrates, niacin, or CETP inhibitors did not define any upper limit of HDL-C for inclusion into the trial (Table 1). No Mendelian Randomization study restricted the analysis to the ranges where changes in HDL-C are associated with changes in risk, e.g. to the lower five or six deciles (Richardson et al. 2020; Voight et al. 2012). Of note, a large register study of a lipid clinics in Boston among individuals with HDL-C below 25 mg/dL (0.8 mmol/L) found an increased prevalence of ASCVD events in carriers of mutations in the genes of APOA1, ABCA1, LCAT, and LPL (Geller et al. 2018). Also studies in Dutch and Canadian families affected by loss of function mutations in APOA1, ABCA1, or LCAT found the prevalence of ASCVD events increased among mutation carriers, but only if HDL-C was below the fifth percentile (Abdel-Razek et al. 2018; Tietjen et al. 2012). Conversely, mutations in the genes of CETP, SCARB1, and LIPG, which cause increases in HDL-C show heterogenous associations with ASCVD. Loss of function mutations in LIPG encoding endothelial lipase do not alter the risk of ASCVD (Voight et al. 2012). The associations of loss of function mutations in CETP and SCARB1 with ASCVD are controversial: Rare

Table 1 The majority of "HDL" trials did not define any cut-off level of HDL cholesterol for inclusion or exclusion of participants

Trial	Drug	Type of prevention	HDL-C inclusion criterion	HDL-C (mmol/L) at baseline
HHS	Gemfibrozil	Primary	Not defined	1.22 ± 0.28
BIP	Bezafibrate	Secondary	<1.16 mmol/L	0.89 ± 0.14
VA-HIT	Gemfibrozil	Secondary	<1.05 mmol/L	0.89 + 0.18
FIELD	Fenofibrate[a]	Diabetes mellitus	Not defined	1.10 ± 0.26
ACCORD[a]	Fenofibrate[a]	Diabetes mellitus	<1.42 mmol/L	0.98 ± 0.21
AIM-HIGH[a]	Niacin[a]	Secondary	<1.05 mmol/L	0.91 ± 0.16
HPS2-THRIVE[a]	Niacin[a]	Secondary	Not defined	1.14 ± 0.30
ILLUMINATE[a]	Torcetrapib[a]	Secondary	Not defined	1.26 ± 0.31
DALOUTCOME[a]	Dalcetrapib[a]	Secondary	Not defined	1.10 ± 0.30
ACCELERATE[a]	Evacetrapib	Secondary	<2.07 mmol/L	1.18 ± 0.30
REVEAL[a]	Anacetrapib	Secondary	Not defined	1.04 ± 0.26

HHS = Helsinki Heart Study (Frick et al. 1987), BIP = Bezafibrate Infarction Prevention (BIP) 2000, VA-HIT (Rubins et al. 1999), FIELD = Keech et al. (2005), ACCORD Study Group (2010); AIM-HIGH Investigators (2011), HPS2-THRIVE Collaborative Group (2014); ILLUMINATE (Barter et al. 2007b), Dal-OUTCOME (Schwartz et al. 2012), ACCELERATE (Lincoff et al. 2017; HPS3/TIMI55–REVEAL Collaborative Group 2017)
[a]Combined with statins vs. statins alone. *HDL-C* HDL cholesterol

SCARB1 mutations were associated with increased CVD risk in one study but not in another (Helgadottir et al. 2018; Zanoni et al. 2016). CETP deficiency was originally associated with reduced risk of ASCVD and increased life expectancy but later studies found diverse associations of loss of function mutations in CETP with ASCVD, namely increased risk in the Honolulu Heart Study but decreased risk in a Japanese population study (Moriyama et al. 1998; Yamashita and Matsuzawa 2016; Zhong et al. 1996). Likewise, the common polymorphisms in CETP which are associated with lower CETP mass and activity, LDL-C, and triglycerides but higher HDL-C were showed diverse associations with ASCVD in different studies: meta-analyses found lower risks of ASCVD associated with loss of function alleles of CETP (Kathiresan 2012; Niu and Qi 2015), but there are several individual studies which found the opposite (Agerholm-Larsen et al. 2000; Borggreve et al. 2006). Loss of function mutations in APOC3 cause higher HDL-C levels and reduce cardiovascular risk (Crosby et al. 2014; Pollin et al. 2008), but this may reflect proatherogenic features of apoC-III beyond its influence on HDL-C and triglyceride levels (Riwanto et al. 2013; Zewinger et al. 2020; Zvintzou et al. 2017) (see also Sect. 3.2).

2.3 Limitations of HDL Modifying Drugs

The futility of the most recent randomized controlled trials (RCTs) on fenofibrate (ACCORD Study Group 2010; Keech et al. 2005), nicotinic acid (AIM-HIGH Investigators 2011; HPS2-THRIVE Collaborative Group 2014), and cholesteryl ester transfer protein (CETP)-inhibitors (ILLUMINATE, Dal-OUTCOME, ACCELERATE, REVEAL) (Barter et al. 2007b; HPS3/TIMI55–REVEAL Collaborative Group 2017; Lincoff et al. 2017; Schwartz et al. 2012) is frequently used as the argument to question the causality of HDL in the pathogenesis of atherosclerosis. However, this conclusion overlooks that – except the CETP inhibitor dalcetrapib (Schwartz et al. 2012) – none of these drugs is specifically altering HDL-C. Especially fibrates and nicotinic acid exert stronger effects on other lipoprotein traits than on HDL-C. Thus, their failure to reduce ASCVD events should primarily prompt to scrutinize the suitability of these pharmacological strategies rather than the causality of HDL in ASCVD. Moreover, one should be oblivious to meta-analyses that demonstrated futility of fibrates or nicotinic acid if combined with statins but efficacy if used as monotherapies (Keene et al. 2014; Riaz et al. 2019). Likewise, genetic studies indicate that potential efficacy of CETP inhibitors in ASCVD prevention may be hampered by the combination with statins (Ference et al. 2017).

2.3.1 Neither Fibrates nor Nicotinic Acid Specifically Target HDL Metabolism

Fibrates are agonists of the peroxisome proliferator agonist receptor alpha (PPARα). As such they regulate the transcription of several genes which are relevant in the metabolism of HDL metabolism (e.g., APOA1, PLTP, SCARB1) but also triglyceride-rich lipoproteins (Montaigne et al. 2021; Zandbergen and Plutzky 2007). As the result, fibrates cause increases in HDL-C of maximally 15% and decreases in triglycerides of 25–50%. The rather moderate effect on HDL-C is partially explained by the induction of APOA1 and SCARB1 genes, which enhances production and catabolism of HDL, respectively. As the result, the flux of HDL and probably reverse cholesterol transport are affected by fibrates more profoundly than reflected by changes in HDL-C. Triglycerides rather than HDL-C were the most profoundly altered lipoprotein traits. The two gemfibrozil utilizing trials – the primary prevention Helsinki Heart Study (Frick et al. 1987) and the secondary prevention study VA-HIT (Rubins et al. 1999) – were the only ones which found significant reductions of ASCVD events by the fibrate intervention vs. placebo. Only three trials (VA-HIT, BIP, and ACCORD) pre-defined plasma levels of HDL-C as inclusion criterion (ACCORD Study Group 2010; Bezafibrate Infarction Prevention Study 2000; Rubins et al. 1999). For ACCORD, the threshold was rather high with 55 mg/dL (1.42 mmol/L) (ACCORD study group 2010). Post-hoc analyses of the fibrate trials demonstrated relative risk reductions for subgroups of patients with HDL-C and triglycerides levels <35 mg/dL (0.9 mmol/L) and >200 mg/dL (2.3 mmol/L) ranging from 27% (FIELD, Keech et al. 2005) to −65% (Helsinki

Table 2 Effects of lipid modifying drug classes on lipoprotein traits and prevention of major cardiovascular events (MACE)

Drug class	LDL-C (max Δ%)	Triglycerides (max Δ%)	HDL-C (max Δ%)	MACE reduction
Statins	−50	−40	+10	Yes
Ezetimibe	−20	−10	0	Yes
Resins	−10	+20	0	Yes
PCSK9-inhibitors	−60	−20	+10	Yes
Fibrates	−10	−40	+15	Controversial: Yes, if without statins or post hoc, if HDL-C low and triglycerides elevated
Omega-3 fatty acids	+10	−35	0	Controversial
Nicotinic acid	−15	−30	+20	Controversial: Yes, if without statins
CETP inhibitors	−40	−15	+130	Anacetrapib: Yes Dalcetrapib & evacetrapib: No Torcetrapib: Adverse

CETP cholesteryl ester transfer protein, *HDL-C* High density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *MACE* major cardiovascular events, *PCSK9* proprotein subtilisin kexin type 9 convertase

Heart Study) (Sacks et al. 2010). Currently the *Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes* (PROMINENT) trial tests prospectively the efficacy of the novel combined PPARα/PPARδ agonist pemafibrate (NCT03071692) (Pradhan et al. 2018).

Nicotinic acid (niacin) is an agonist of the G-protein coupled receptor GPR109A (HM74A or PUMA-G) (Offermanns 2014). As such, it primarily inhibits the lipolysis in adipocytes and secondarily, by reducing the free fatty acid flux, the lipogenesis and VLDL production in the liver. Reduced free fatty acid exposure may also promote ABCA1 activity in the liver and hence the production of nascent HDL (Chapman et al. 2010; KAmanna et al. 2013). In addition CETP activity was found decreased upon treatment with nicotinic acid due to direct and indirect inhibitory effects via production as well as activity of the protein and diminished pool of VLDL and hence acceptor particles, respectively (Chapman et al. 2010). In addition, nicotinic acid lowers plasma levels of LDL-C and lipoprotein(a) (Lp(a)). Despite these multiple beneficial effects on lipoproteins, in both the AIM-HIGH and HPS-THRIVE trials, the combination of statins with nicotinic acid was not superior to statin monotherapy in preventing ASCVD events (Table 2) (AIM-HIGH Investigators 2011; HPS2-THRIVE Collaborative Group 2014). Only AIM-HIGH defined inclusion criteria based on HDL-C (<1.05 mmol/L or <40 mg/dL). However, post-hoc analyses did not find any evidence that low HDL-C defines a subgroup of patients who benefit from nicotinic acid (Guyton et al. 2013; HPS2

THRIVE Collaborative Group 2014) However, in a meta-analysis monotherapy of nicotinic acid was found effective in reducing cardiovascular morbidity and mortality (Keene et al. 2014). Because of futility and the occurrence of flushes as very unpleasant and frequent side effects, nicotinic acid is no longer available for treatment in many countries.

2.3.2 CETP Inhibitors Block Rather than Promote Reverse Cholesterol Transport

CETP links the metabolism of HDL and apoB containing lipoproteins by exchanging cholesteryl esters of HDL against triglycerides of VLDL and LDL (Chapman et al. 2010). As the result of inhibiting this exchange, the most effective CETP inhibitors – torcetrapib, evacetrapib, and anacetrapib – cause increases of HDL-C by 75 (Torcetrapib) to 130% (Evacetrapib) and decreases of LDL-C by 25% (torcetrapib) to 40% (Anacetrapib) (Barter et al. 2007b; HPS3/TIMI55–REVEAL Collaborative Group 2017; Lincoff et al. 2017). The weaker CETP inhibitor dalcetrapib increases HDL-C by 30% without causing any drop in LDL-C (Schwartz et al. 2012). CETP inhibitors also decrease Lp(a) by up to 35% through an as yet unknown mechanism (Gencer and Mach 2020). Despite their at first sight beneficial effects on lipoprotein traits, three trials were prematurely stopped; the ILLUMINATE trial because of excess morbidity and mortality in the torcetrapib arm possibly due to off target effects of torcetrapib (Barter et al. 2007b). ACCELERATE and dal-OUTCOME were stopped prematurely because of futility of evacetrapib and dalcetrapib, respectively (Lincott et al. 2017; Schwartz et al. 2012). Only the combination of statin with anacetrapib in the REVEAL trial showed some superiority towards statin only therapy (HPS3/TIMI55–REVEAL Collaborative Group 2017). However, with a 9% relative risk reduction or the primary endpoint, the added value of anacetrapib was small and attributed to the decrease in LDL-C rather than to the increase in HDL-C. Because of the parallel successful development of PCSK9 inhibitors, which are much more effective in lowering LDL-C and event rates, the development of anacetrapib was stopped. Dalcetrapib, however, is further developed towards a personalized indication: post-hoc analyses of the Dal-OUTCOME study revealed that the carrier status for a mutation in the adenylate cyclase subtype 9 encoding ADCY9 gene discriminated individuals who did or did not benefit from dalcetrapib treatment by lower ASCVD event rates (Tardif et al. 2015). However, the same mutation discriminated responders and non-responders neither to anacetrapib nor to evacetrapib in the REVEAL and ACCELERATE trials, respectively (Hopewell et al. 2019; Nissen et al. 2018). Conversely, the interaction of CETP with ADCY9 was recapitulated in genetic mouse models (Rautureau et al. 2018). The Dal-GenE trial currently investigates prospectively, whether patients selected for the ADCY9 genotype benefit from treatment with dalcetrapib (NCT02525939) (Tardif et al. 2020).

At first sight the negative outcomes of the CETP inhibitor trials were surprising, not only because of the beneficial effects on the lipoprotein profile but also because several large genetic studies demonstrated lower prevalences or incidences of cardiovascular events among carriers of low activity CETP alleles (Kathiresan

2012). However, later population genetic studies showed an interaction between CETP and HMGCR alleles. In the presence of HMGCR alleles that reduce HMG-CoA reductase activity and thereby mimic treatment effects of statins, CETP alleles that cause low CETP activity and mimic the effects of CETP inhibitors did not confer any additional cardiovascular risk reduction (Ference et al. 2017). Likewise, torcetrapib treatment reduced atherosclerosis in apoE3 Leiden*CETP transgenic mice, if provided as monotherapy but not if provided in combination with statins (de Haan et al. 2008) whereas anacetrapib treatment enhanced the anti-atherogenic effect of atorvastatin (Kühnast et al. 2015). Nevertheless, the question is raised if the anti-atherogenicity of CETP inhibition depends on the capacity of the LDL receptor pathway: if this is fully functional, for example, as the result of statin treatment, CETP will promote reverse cholesterol transport and should not be blocked (von Eckardstein 2020). Only in situations, where LDL removal by the LDL receptor pathway is compromised, it may be useful to withheld cholesterol from LDL by CETP inhibition for hepatic removal through LDL receptor independent pathways involving direct HDL/receptor interactions, for example with SR-BI. As an alternative explanation, it was proposed that CETP inhibition renders HDL dysfunctional by prolonging the half-life of HDL particles and thereby making them susceptible to adverse alterations in the lipid and protein composition or oxidative and enzymatic modifications of protein or lipid components. However, the classical function of HDL, mediation of cholesterol efflux from macrophages was rather increased upon treatment of humans or animals with Evacetrapib, Anacetrapib, or Dalcetrapib (Brodeur et al. 2017; Metzinger et al. 2020; Nicholls et al. 2015; Simic et al. 2017; Tardif et al. 2015). Interestingly endothelial functions were not improved or even impaired in apoE3 Leiden*CETP transgenic mice upon treatment with evacetrapib and anacetrapib, respectively, despite increasing CEC and paraoxonase activity (Simic et al. 2017).

2.3.3 Combination with High-Intensity Statins: The Winner Takes it All

The combination of statins with fenofibrate, nicotinic acid, or CETP inhibitors was motivated by post-hoc meta-analyses of statin trials, which found the residual risk of patients treated with statins to be significantly associated with low HDL-C levels (Boekholdt et al. 2013). A closer look to post-hoc analyses of individual trials, however, reveals that these associations became weaker the lower LDLC levels were reached. For example, in the WOSCOP study, where mean levels of LDL-C were lowered from 5.0 mmol/L in the placebo arm to 3.6 mmol/L in the pravastatin arm, low baseline levels of HDL-C were associated with increased risk of ASCVD events in both treatment groups (West of Scotland Coronary Prevention Study Group 1998). However, more than 10 years later in the JUPITER study (LDL-C at baseline $<$3.37 mmol/L), both baseline and on-treatment levels of HDL-C were significantly associated with residual risk only in the placebo group with a mean on treatment LDL-C of 2.8 mmol/L, but not in the rosuvastatin group with an on treatment mean LDL-C level of 1.42 mmol/L (Ridker et al. 2010). Similar discrepant observations were made in the secondary prevention trials CARE and LIPID vs. TNT: HDL-C levels explained part of the residual risk in both placebo and pravastatin groups of

CARE and LIPID (mean baseline LDL-C 3.80 mmol/L, on treatment LDL-C 2.85 mmol/L) (Sacks et al. 2000). However, in the TNT trial (baseline LDL-C 2.55 mmol/L), low HDL-C increased ASCVD risk in the low-dose atorvastatin group (on treatment LDL-C 2.60 mmol/L) but not in the high dose atorvastatin group (on treatment LDL-C 2.0 mmol/L) (Barter et al. 2007a). It thus appears that the optimized control of LDL-C by high intensity statin therapy alleviates the residual risk associated with low HDL-C levels. In this regard it is also noteworthy that contemporary observational studies in general populations as well as in patients with clinically manifest ASCVD find weaker associations of HDL-C with first and recurrent cardiovascular events, respectively, than historical studies which recruited their participants in the pre-statin era (Bolibar et al. 2000; Colantonio et al. 2016; Schwartz et al. 2012). These secular trends are usually explained by the generally improved risk factor control. However, one must also be aware of the change in the methodology of HDL-C measurements that occurred in parallel with the triumphal procession of statins. Since about 1990, non-traceable and biased homogenous assays have replaced the previous cholesterol quantification after manual precipitation of apoB containing lipoproteins. One can hence not exclude that changes in the analytics affected the prognostic value of HDL-C (Miller et al. 2010).

2.4 Wrong Biomarker "the Good Cholesterol"

By contrast to the disease causing cholesterol in LDL (Borén et al. 2020), the cholesterol in HDL (that is HDL-C) neither exerts nor reflects any of the potentially anti-atherogenic activities of HDL. HDL-C is only a non-functional surrogate marker for estimating the HDL pool size without deciphering the heterogeneous composition and, hence, functionality of HDL (Rohatgi et al. 2021; Annema and von Eckardstein 2013, 2016). Differences in the molar content of apoA-I, phosphatidylcholines, cholesterol, and cholesteryl ester cause differences of HDL subclasses in shape, size, and charge. HDL particles carry hundreds of different quantitatively minor proteins and lipid species many of which are not just passive cargo (like cholesterol) but biologically active and susceptible to quantitative and qualitative modifications by diseases or interventions (Rohatgi et al. 2021, Annema and von Eckardstein 2013, 2016). These functionally active components hence have a much bigger chance than HDL-C to serve as a causal biomarker that can be exploited towards the development, targeting, and monitoring of therapies.

The most obvious candidate for a functional HDL biomarker is the plasma concentration of apoA-I which is not only a mandatory structural component of the bulk of HDL but also exerts several biological activities of HDL, for example activation of ABCA1 and LCAT to efflux and esterify cholesterol, respectively, or binding to SR-BI and other HDL receptors. In both epidemiological and clinical studies, apoA-I levels show inverse associations with ASCVD events, which however are not stronger than those of HDL-C (Emerging Risk Factors Collaboration 2009). Neither did Mendelian Randomization studies unravel any causal genetic

relationship between apoA-I levels and ASCVD (Karjalainen et al. 2020; Richardson et al. 2020).

Other widely investigated HDL biomarker candidates include numbers and sizes of HDL particles. However, the outcomes of their evaluation in epidemiological and clinical studies are controversial. Some studies found HDL particle number (HDL-P) superior to HDL-C (Chandra et al. 2015; Kuller et al. 2007; Mackey et al. 2012; Otvos et al. 2006; Singh et al. 2020), others vice versa (El Harchaoui et al. 2009; Mora et al. 2009; Parish et al. 2012; Qi et al. 2015). Interestingly, within the JUPITER trial HDL-P was superior to HDL-C in the prediction of events among statin treated probands but inferior among placebo treated probands (Mora et al. 2013). Some studies found small HDL particles more strongly related with outcomes than large HDL particles (Ditah et al. 2016; Kim et al. 2016; McGarrah et al. 2016; Silbernagel et al. 2017), other studies found the opposite (Li et al. 2016; Arsenault et al. 2009). A recent meta-analysis of four studies concluded similar strong associations of small, medium, and large HDL particles with the incidence of ASCVD events (hazard ratio and 95% confidence interval 0.91 and 0.87 to 0.96) (Wu et al. 2018). With a hazard ratio and 95% confidence interval of 0.82 and 0.78 to 0.87, the total number of HDL particles showed stronger associations. Interestingly a recent Mendelian Randomization study found protective associations between the concentration of medium and – less so but also significantly – small HDL particles with coronary artery disease (Zhao et al. 2021). Drug interventions in lipoprotein metabolism result in diverse changes of HDL particle size and numbers. For example, treatment with nicotinic acid and CETP inhibitors increases HDL-C levels more profoundly than HDL-P, reflecting the shift to larger particles. Vice versa, upon treatment with fibrates, HDL-P increases more strongly than HDL-C (Rosenson et al. 2015).

3 Consequences and Perspectives

3.1 The Search for Novel HDL-Biomarkers

The further development of HDL as a therapeutic target is mainly limited by the availability of biomarkers that reflect the functional and causal role of HDL in the pathogenesis of atherosclerosis. To this end, bioassays of HDL function were recently developed and validated in population and clinical studies. Among them, cholesterol efflux capacity (CEC) has been investigated most extensively. In these studies, different macrophage cell lines treated with different drugs to enhance the cellular cholesterol efflux machinery were utilized as donors of radioactively or fluorescently labeled cholesterol. ApoB depleted plasma or serum was used as acceptors and as surrogate of HDL to avoid laborious ultracentrifugation. The heterogeneity of assays together with the heterogeneity of populations investigated has contributed to some discrepant findings (Anastasius et al. 2018). Nevertheless, a recent meta-analysis of eight prospective studies and more than 10,000 participants with more than 3,000 events found a significant inverse association of CEC with

ASCVD events (HR 0.86, 95% CI: 0.76–0.98). In a subgroup of five studies also mortality was related to CEC (HR 0.77, 95% CI: 0.80–1.0). Although CEC correlates with HDL-C, the associations of CEC with cardiovascular outcomes were independent of HDL-C (Soria-Florido et al. 2020). However, the concept of CEC as a proxy of HDL functionality has several limitations. First, as a laborious and difficult if not impossible to standardize bioassay it is a research rather than diagnostic tool, primarily for proof of concept studies and secondarily for the identification of functional molecular markers (Anastasius et al. 2018). Second, CEC should not be considered as an overall proxy of HDL functionality because other functions of HDL neither correlate nor share molecular determinants with CEC (Cardner et al. 2020). Third, although most intensively investigated, it is not clear that mediation of cholesterol efflux is the most relevant atheroprotective function of HDL. In fact, changes in CEC upon treatment with CETP inhibitors did not predict correctly the clinical outcomes of these drug interventions. They led to increases in CEC of apoB-free sera or plasmas but not to any reduction in cardiovascular event rates and coronary atherosclerosis, respectively (Brodeur et al. 2017; Metzinger et al. 2020; Nicholls et al. 2015; Simic et al. 2017; Tardif et al. 2015).

Despite these limitations, CEC has been used as the reference to develop molecular biomarkers that can be measured in clinical laboratories. One example is the derivation of an algorithm which integrates the information of differently sized HDL particles as measured by NMR. The estimated NMR-based CEC correlated very well with the in vitro measured CEC ($R^2 > 0.8$) and predicted incident CHD events with a hazards ratio of 0.86; 95% CI, 0.79–0.93, adjusted for traditional risk factors and HDL-C) (Kuusisto et al. 2019). Another example is a proteomic score integrating the information of apolipoproteins A-I, C-I, C-II, C-III, and C-IV showed good correlation with CEC as well as significant association with the presence of coronary artery disease and cardiovascular mortality independently of clinical risk factors including conventionally measured concentrations of apoA-I and apoB (Jin et al. 2019; Natarajan et al. 2019). Replication studies are needed to validate these surrogate scores of CEC.

Several laboratories have used tandem mass spectrometry to search for protein or lipid components of HDL as functional biomarkers. The most recent update of the HDL Proteome Watch data bank (http://homepages.uc.edu/~davidswm/HDLproteome.html; accessed July 15, 2021) documents more than 200 proteins which were identified in HDL by at least three of 40 independent studies and are therefore considered as highly confident components of HDL. Even higher numbers of lipid species were identified by mass spectrometry of HDL (Cardner et al. 2020; Kontush et al. 2013). The concentrations of these molecules vary from less than 1 μmol/L to more than 1 mmol/L (Annema and von Eckardstein 2013; Rohatgi et al. 2021). Already in view of the average HDL particle concentration of about 20 μmol/L it is clear that only some lipids (e.g., unesterified cholesterol, cholesteryl esters, phosphatidylcholines) or proteins (e.g., apoA-I) are present on each particle with several copies. Other low abundant lipids (e.g., sphingosine-1-phosphate, oxysterols) and proteins (apoM or LCAT) are dispersed throughout different particles. Interestingly, these molecules are non-randomly distributed among HDL

particles. For example, the presence of sphingosine-1-phosphate is linked to the presence of its chaperone apoM (Christoffersen et al. 2011). By combining two immunoaffinity chromatography procedures, one with anti-apoA-I antibodies and one with an antibody against one of 16 other HDL-associated proteins, 16 HDL subclasses with distinct proteomes and little intraindividual variation over 3–-24 months were identified (Furtado et al. 2018). Many proteins of each HDL subspecies exert related functions, for example in lipid transport, hemostasis, oxidation, or inflammation suggesting that specific functions beyond cholesterol efflux are exerted by distinct subspecies of HDL rather than the bulk of HDL. In agreement with this concept, a recent systems biology approach found distinct functions of HDL determined by clusters of distinct proteins and lipids carried by HDL with little overlap between the functions (Cardner et al. 2020). Moreover, in four prospective nested case–control studies, the presence or absence of distinct proteins was found to determine the association of apoA-I levels with incident cardiovascular events (Sacks et al. 2020). For example, apoA-I levels in particles that contain apoE or apoC-I but not their apoE or apoC-I- free counterparts showed the expected inverse association with incident ASCVD events. Vice versa, apoA-I levels in apoC-III-free particles but not particles containing apoC-III showed the expected inverse association with incident ASCVD events (Sacks et al. 2020). Cholesterol levels in apoC-III containing HDL even showed a positive association with incident ASCVD (Jensen et al. 2018). Moreover, apoC-III containing HDL was found to interfere with the capacity of HDL to inhibit the apoptosis of endothelial cells and to promote efflux from macrophages (Riwanto et al. 2013; Zvintzou et al. 2017). This makes apoC-III an interesting target for therapy beyond lowering of triglycerides (Zewinger et al. 2020). Other studies found the enrichment of HDL with either pulmonary surfactant protein B or serum amyloid protein A associated with increased risk of mortality in patients with diabetic end-stage nephropathy, heart failure, or CHD (Emmens et al. 2018; Kopecky et al. 2015; Zewinger et al. 2015).

Several mass spectrometric studies demonstrated gross alterations in the lipidome of HDL in patients with acute or chronic CHD as well as changes in response to statin therapy or body weight reduction (Cardner et al. 2020; Khan et al. 2018; Meikle et al. 2019; Orsoni et al. 2016; Sutter et al. 2015). However, to date, only signatures of lipid species in total plasma but not in HDL have been explored for their prognostic performance in prospective studies (Hilvo et al. 2019; Mundra et al. 2016). NMR-based studies identified some more general lipid traits of HDL to be associated with incident disease. However, they represent classes or subclasses rather than species of lipids and they are strongly intercorrelated with each other as well as measures of particle size or numbers so that they are not pursued as biomarkers beyond the latter indices (Cardner et al. 2020; Hafiane and Genest 2015; Rosenson et al. 2011).

3.2 Ongoing and Novel Drug Developments

After the failure of CETP inhibitors, only few drug developments targeting HDL have been continued or newly started. Some of the latter targets are pleiotropic and HDL is a bystander rather than the focus of these drug developments.

3.2.1 Reconstituted HDL, apoA-I Mimetic Peptides, and Recombinant LCAT

After infusions of artificially reconstituted HDL (rHDL) were found to reduce atherosclerosis in hypercholesterolemic rabbits, several formulations of rHDL were developed for investigation of their atheroprotective effects (He et al. 2021. Because rather large amounts of protein are needed, only short-term applications in acute clinical settings are feasible, for example in patients with acute coronary syndrome (ACS). rHDL containing phosphatidylcholines together with the recombinant apoA-I Milano variant (ETC-216, MDCO-216) or recombinant wild type apoA-I plus sphingomyelin (Cer001) or apoA-I isolated from plasma (CSL111, CSL112) were initially tested in phase II trials for their short-term effects on coronary atherosclerosis which was assessed by intravascular ultrasound of ACS patients. Whereas initial studies showed some regression of coronary atherosclerosis upon treatment with ETC.-216 or CSL111 (Tardif et al. 2007; Nissen et al. 2003), later larger studies with MDCO-216 or Cer001 did not (Nicholls et al. 2018a, b). Neither did Cer001 cause regression or prevent progression of carotid atherosclerosis in patients with genetic HDL deficiency (Zheng et al. 2020). Currently only one formulation – CSL112 – is further pursued by a large randomized and controlled phase III trial (ApoA-I Event Reducing in Ischemic Syndrome II = AEGIS II). Seventeen thousand four hundred patients with myocardial infarction are randomized to 4 weekly infusions of either 6 g CSL112 or placebo within 5 days of the event (Gibson et al. 2021). The primary outcome is the time to first occurrence of the composite of CV death, MI, or stroke through 90 days. Secondary outcomes include the total number of hospitalizations for coronary, cerebral, or peripheral ischemia through 90 days and time to first occurrence of the composite primary outcome through 180 and 365 days. Results are expected to become available in 2023.

In addition to rHDL containing full length apoA-I, also apoA-I mimetic peptides are developed for treatment of atherosclerosis. They showed promising results in vitro and in preclinical animal models. Three of them have been tested for safety and effects on HDL-C and HDL function. For two of them – L4F and D4F – results have been reported. They did not cause any changes in HDL-C or anti-inflammatory HDL functions. No results have been reported for ETC642. The clinical development of FX-5A is planned (Wolska et al. 2021).

Application of recombinant LCAT is an alternative strategy to increase HDL-C or promote HDL metabolism by substitution of components (Freeman et al. 2020). In a randomized controlled study 32 patients were treated with three weekly injections of different dosages of recombinant LCAT (MEDI6012) or placebo (Bonaca et al. 2021). Compared to placebo, MEDI6012 caused dose-dependent increases of

HDL-C by 66% to 144% at day 19. Interestingly the initial bolus injection led to a more than 40% increase of HDL-C within 30 min. MEDI6012 caused neither any severe side effects nor the generation of neutralizing antibodies. In an ongoing phase IIb trial (REAL-TIMI 63B), the application of 2 dosages of MEDI6012 to ACS patients is currently investigated for its effect on infarct size in more than 400 ACS patients (https://clinicaltrials.gov/ct2/show/NCT03578809). Half of the patients receive additional 4-weekly injections of MEDI6012 or placebo for 12 weeks for investigation of LCAT's effects on coronary calcification. Of note, recombinant LCAT is also attractive for the use as enzyme replacement in familial LCAT deficiency, however with the goal to prevent the development and progression of nephropathy in these patients (Freeman et al. 2020; Vaisman et al. 2019).

3.2.2 Apabetalone

Apabetalone (RVX208) is an inhibitor of bromodomain and extraterminal (BET) proteins that regulate the expression of multiple genes by interference with histone acetylation. RVX208 was initially developed because it strongly induced APOA1 gene expression in cultivated hepatocytes and caused a profound increase of HDL-C and apoA-I levels in non-human primates by 90 and 60%, respectively (Ghosh et al. 2017). Also mice responded with substantial increases of HDL cholesterol. Atherosclerosis was suppressed in apoE deficient mice. However, in humans treatment with apabetalone caused very moderate increases in HDL-C and apoA-I levels but also reduced CRP levels. The development of the drug was stopped after a recent phase III trial (BETonMACE) in patients with acute coronary syndrome and type 2 diabetes did not reveal any reduction of clinical events compared with placebo. (Ray et al. 2020).

3.2.3 PPAR Modulators

The PPARa modulator Pemafibrate is developed primarily for the treatment of hypertriglyceridemia and the related cardiovascular risk. In a phase II dose finding study, pemafibrate dose-dependently decreased triglycerides and increased HDL-C by up to 42% and 21%, respectively, compared to 30% and 14% by fenofibrate (Arai et al. 2017). In hypertriglyceridemic patients, treatment with pemafibrate caused increases of HDL-C by about 16% as well as CEC (Yamashita et al. 2018). In apoE2 knock-in mice, pemafibrate increased HDL-C, CEC as well as macrophage-to-feces reverse cholesterol transport, and reduced the extent of atherosclerotic lesions (Hennuyer et al. 2016). The PROMINENT trial investigates the effect of pemafibrate vs. placebo on cardiovascular outcomes of 10,000 participants with diabetes mellitus type 2, triglycerides 200–499 mg/dL (2.26–5.64 mmol/L), HDL-C level $\leq$40 mg/dL(1.03 mmol/L) during a maximal follow-up of 5 years (Pradhan et al. 2018).

3.2.4 ANGPTL3 and Endothelial Lipase

Angiopoietin-like protein 3 (ANGPTL3) is mainly produced by the liver and an endogenous inhibitor of both lipoprotein lipase and endothelial lipase (EL). After the discovery of loss of function mutations in the ANGPTL3 gene as a cause of

panhypolipoproteinemia and reduced cardiovascular risk (Arca et al. 2020), antisense oligonucleotides as well as monoclonal antibodies were developed for the treatment of hypertriglyceridemia and hypercholesterolemia. In fact, treatment of hypertriglyceridemia with the antisense oligonucleotide Vupanorsen and refractory hypercholesterolemia with the monoclonal antibody Evinacumab caused pronounced decreases of triglyceride levels and LDL-C but also HDL-C (Gaudet et al. 2020; Rosenson et al. 2020) The clinical implication of the 20–30% decrease in HDL-C is not known but very likely reflects the increased activity of EL upon ANGPTL3 inhibition (Wu et al. 2020).

Conversely, also EL inhibitors are developed with the aim to increase HDL-C. Treatment of non-human primates with the monoclonal anti-EL antibody MEDI5884 dose-dependently increased HDL-C and apoA-I levels by up to 100% and 30%, respectively (Le Lay et al. 2021). In a phase I study, human volunteers also experienced increases in HDL-C and apoA-I as well as particle number and size. CEC and anti-inflammatory activities of HDL were also improved. However, endothelial lipase inhibition also caused increases in LDL-C, albeit more profoundly in non-human primates than in humans. In non-human primates this unwanted effect could be blocked by PCSK9 inhibition. Nevertheless, one must wonder whether the risk of increasing LDL-C is well taken, especially since loss-of-function alleles of LIPG encoding EL do not confer any cardiovascular risk reduction despite increasing HDL-C thus questioning the clinical utility of EL inhibition (Voight et al. 2012).

3.2.5 ApoC-III Inhibition

Antisense oligonucleotides against apoC-III (Volanesorsen) exert pronounced triglyceride lowering effects by reducing the production of VLDL as well as by promoting lipolysis and remnant removal by disinhibiting lipoprotein lipase and remnant receptors, respectively. Probably secondarily to the lowering of triglycerides, interference with apoC-III in patients with chylomicronemia also leads to increases of HDL-C levels by 40% (Witztum et al. 2019). Although not tested, one must assume that Volanesorsen also decreases the content of apoC-III in HDL. In view of the positive rather than inverse association of apoC-III containing HDL with cardiovascular outcomes (Jensen et al. 2018; Sacks et al. 2020); as well as the noxious effects of apoC-III on HDL functionality towards cholesterol efflux and endothelial survival and inflammation (Riwanto et al. 2013; Zewinger et al. 2020; Zvintzou et al. 2017), one may hypothesize that apoC-III inhibition also exerts antiatherogenic effects by improving HDL function. However, this hypothesis needs to be tested.

3.2.6 HDL-C Lowering Therapies: Probucol and Androgens

For a long time, lowering of HDL-C has been considered as a safety issue in drug development. This has changed as the causal role of HDL in ASCVD has been questioned. Even more so, the association of high HDL-C with increased mortality and morbidity for certain diseases (Bowe et al. 2016a; Ko et al. 2016; Madsen et al. 2017) raises the question whether under certain conditions HDL-C lowering may be useful. In view of the genetic association of loss of function mutations in SR-BI with

increased cardiovascular risk (Zanoni et al. 2016) and the finding of increased atherosclerosis in Scarb1 knock-out mice (Hoekstra and van Eck 2015), especially therapies that lower HDL-C by upregulation of SR-BI in the liver may be interesting.

Probucol is an old drug which was originally developed to exploit its anti-oxidative effects on LDL. Although it was shown to induce regression of atherosclerosis and xanthomas and has been rather widely used in Japan, the development and clinical application of probucol has not been consequently pursued (Yamashita et al. 2015). The main reason was the about 30% lowering of HDL-C. Activation of CETP and SR-BI has been elucidated as the underlying mechanism. In the most recent PROSPECTIVE trial, 876 Japanese patients with CHD and LDL-C $\geq$140 mg/dL without medication or those treated with lipid-lowering drugs received optimal lipid-lowering treatment together with placebo or probucol 500 mg/day. After 3 years, LDL-C and HDL-C were 8.5 mg/dL and 16.3 mg/dL, respectively, lower in the probucol than in the placebo group. The event rates did not differ significantly between the groups, although by trend, CHD events happened less frequently in the probucol group (Arai et al. 2021). Interestingly, the combined analysis of the PROMINENT and IMPACT trials showed reductions of cerebrovascular events, however in the absence of any effect on carotid atherosclerosis (Yamashita et al. 2021). Although futile, the data raise the question of whether probucol is a treatment option for patients with high HDL-C.

The stimulatory effects of testosterone on hepatic SR-BI expression are probably the main reasons for the substantial differences in HDL-C levels between males and females (Chiba-Falek et al. 2010; Langer et al. 2002). Even more so, the HDL-lowering effects of testosterone have contributed to the caution on the use of testosterone for the treatment of the aging male syndrome, transgender patients, or female sexual dysfunction as well as for male contraception (Thirumalai et al. 2015; Wu and von Eckardstein 2003). The effects of testosterone replacement on hard cardiovascular endpoints have not been investigated. However, a recent randomized controlled trial in 1007 men with overweight or obesity as well as disturbed or manifest diabetes at baseline showed benefits of 1,000 mg intramuscular testosterone vs. placebo injection on glycemic control and incidence of diabetes during 2 years of follow-up (Wittert et al. 2021).

3.3 Other Disease Targets

As late onset diseases, ASCVDs have not been rate limiting in the evolution of species. Therefore, one must envisage that the broad spectrum of HDL's protective functions has rather evolved to prevent other diseases or secure survival and healing of their victims. Such diseases or their clinical complications may serve as more appropriate targets than ASCVD for the therapeutic exploitation of HDL (Von Eckardstein and Rohrer 2016). Indeed, recent epidemiological and genetic studies unraveled several associations of HDL-C and genetic loci intimately related to HDL metabolism with non-cardiovascular diseases as well as mortality (Table 3) (Kjeldsen et al. 2021a; Madsen et al. 2021). Please note the diverse directions of

Table 3 Role of HDL in different diseases according to epidemiology, therapeutic interventions, human genetics, and animal experiments

Diseases	Association in observational studies	Clinical benefit in intervention studies	Genetic association	Animal experiments
Atherosclerotic cardiovascular diseases	Discontinuously inverse (until 60th percentile)	No (CETP inhibitors) or subgroups (fibrates)	No	Gene-dependent
Diabetes	Inverse	(yes) (post-hoc: CETP inhibitors, rHDL)	Yes (Mendelian gene scores) No (candidate genes)	Yes (ABCA1, APOA1)
Chronic kidney disease	Parabolic	Not investigated	Yes	Yes (LCAT)
Infections	Parabolic	Not investigated	Yes	Yes (APOA1, CETP, rHDL)
Autoimmune disease	Inverse	Not investigated	Not investigated	Yes (APOA1, SCARB1, S1P)
Age-related macular degeneration	Positive	Not investigated	Yes	(Yes) (ABCA1)
Alzheimer's disease	Discontinuously positive (>95th percentile)	Not investigated	No (Mendelian gene scores) Yes (GWAS, e.g., ABCA1)	(Yes) (ABCA1)

these associations which reach from inverse (diabetes, autoimmune diseases) over parabolic (infections, chronic kidney disease, mortality) to positive (Alzheimer's disease, age related macular degeneration), re-emphasizing that the kinetics of HDL metabolism and HDL function rather than the concentration of HDL particles are relevant.

3.3.1 Diabetes

Low levels of HDL-C are frequent in patients with diabetes mellitus type 2. This finding even precedes the manifestation of hyperglycemia and is hence an indicator of increased risk for incident diabetes (Haase et al. 2015; Schmidt et al. 2005; von Eckardstein et al. 2000; White et al. 2016; Wilson et al. 2007). Because of multiple effects of insulin on HDL metabolism, most of which are indirect via free fatty acids

or triglyceride-rich lipoproteins, these associations have been explained for a long time by reverse causality: diabetes and pre-diabetes cause low HDL-C rather than vice versa (Parhofer 2015; Vollenweider et al. 2015; von Eckardstein and Widmann 2014). However, increasing evidence from in vitro as well as in vivo studies indicates that HDL exerts protective functions on the function and survival of pancreatic beta cells as well as on the sensitivity of target cells to insulin (Cochran et al. 2021; Manandhar et al. 2020; Vollenweider et al. 2015; von Eckardstein and Widmann 2014; Yalcinkaya et al. 2020). Also mitochondrial function and thereby cellular energy metabolism is modulated by HDL (Lehti et al. 2013). In humans, the potentially anti-diabetic effects of HDL are best illustrated by the acute glucose lowering effect of rHDL infusion (Drew et al. 2009) as well as by the findings of post-hoc analyses of the CETP inhibitor trials: Participants who received the CETP inhibitors showed better glycemic control and experienced less often new-onset diabetes as compared to the placebo treated controls (Barter et al. 2011; Masson et al. 2018; Menon et al. 2020; Schwartz et al. 2020). Mendelian randomization studies yielded controversial results on the genetic causality of HDL-C in diabetes (Fall et al. 2015; Haase et al. 2015; White et al. 2016).

3.3.2 Chronic Kidney Disease

The Veterans Administration study showed a parabolic association of HDL-C with >30% declining estimated glomerular filtration rate (eGFR) or the incidence of eGFR <60 ml/min and also provided evidence for genetic causality (Bowe et al. 2016b). Mutations in APOA1, APOE; APOL1, and LCAT are causes of genetic nephropathies (Strazzella et al. 2021). However, it is not clear whether their pathogenesis involves HDL: Certain missense mutations in APOA1 cause familial amyloidosis, which also affect other organs (Zanoni and von Eckardstein 2020). Specific mutations in APOE cause lipid glomerulopathy which however has been suggested to develop in response to disturbed interactions of apoB containing lipoproteins with the LDL receptor or due to accumulation of the structural defective apoE (Saito et al. 2020). ApoL1 is the trypanolytic factor which is transported by a minor subfraction of HDL (Friedman and Pollak 2020). Certain apoL1 variants that protect the host from infections with Trypanosoma brucei rhodesiense and gambiense dramatically increase the risk of chronic kidney disease, notably focal segmental glomerulosclerosis, in their African and Afroamerican carriers (Friedman and Pollak 2020). LCAT deficiency is a classical HDL deficiency syndrome causing a nephropathy that eventually progresses to end-stage renal disease (Pavanello and Calabresi 2020). However, the pathogenic mechanism depends on the accumulation of lipoprotein X rather than the absence of HDL (Vaisman et al. 2019). This is best illustrated by the absence of nephropathy in patients with fish-eye disease where partial loss of LCAT causes the same decrease in HDL as classical LCAT deficiency, however no nephropathy (Pavanello and Calabresi 2020).

Treatment with fibrates improves albuminuria but worsens glomerular filtration rate (Speer et al. 2021). Niacin has no effect on renal function. Small studies also indicate protective effects of probucol towards acute kidney injury, for example of patients exposed to contrast agents (Xin et al. 2019). The pleiotropic effects of these

drugs on lipoprotein metabolism and the lack of association between changes in renal function and HDL-C under their treatment do not allow any conclusion on the role of HDL modifying therapies for prevention or treatment of CKD. Furthermore the exploitation of HDL towards kidney disease is also hampered by the currently unknown mechanisms how HDL exerts renal protection by HDL. Since small HDL particles are undergoing glomerular filtration and tubular re-uptake by the megalin/cubilin co-receptors, it may be that HDL delivers protective molecules to the kidney, for example sphingosine-1-phosphate (Bisgaard and Christoffersen 2019; Strazzella et al. 2021).

3.3.3 Infections

The Copenhagen General Population study found U-shaped associations between HDL-C and the incidence of infections (Madsen et al. 2018). The associations with bacterial infections were stronger than with viral infections. Upon limited adjustment, gastroenteritis, bacterial pneumonia, skin and urinary tract infections, as well as sepsis were more prevalent among individuals with HDL-C <1.0 mmol/L as compared to individuals with higher HDL-C. Upon full adjustment the associations with gastroenteritis and pneumonia remained significant (Madsen et al. 2018). A preliminary Mendelian randomization analysis with two loci (CETP and LIPC) provided initial evidence of genetic causality (Madsen et al. 2018). Genetic causality also exists for the association of low HDL-C with the incidence of sepsis as well as with the chance of survival in patients with sepsis (Trinder et al. 2020). Evidence from population studies as well as experiments in genetic animal models points to the importance of CETP in this process (Blauw et al. 2020; Trinder et al. 2019, 2021). However also HDL particles per se as well as specific structural components of HDL exert several antibacterial activities such as binding and removal of lipopolysaccharides, protection of epithelial and endothelial barriers, or modulatory effects on leukocyte functions (Catapano et al. 2014; Meilhac et al. 2020; Pirillo et al. 2015; Robert et al. 2021; Rohatgi et al. 2021; Trakaki and Marsche 2021). The special association of HDL-C with gastroenteritis may also mirror an important role of HDL that is locally produced in the intestine (Ko et al. 2020). Similarly, the protection from pneumonia may mirror the high exposure of the lung to newly synthesized HDL due to first pass effects (Gordon et al. 2016). In sepsis models, genetically modified mice overexpressing human apoA-I showed improved survival (Meilhac et al. 2020; Morin et al. 2015). Interestingly, the clinical development of CSL111 was originally aiming at the treatment of sepsis since their infusion into volunteers exerted several beneficial effects on inflammation, coagulation, and fibrinolysis (Pajkrt et al. 1996, 1997). Most recent experiments in preclinical sepsis models demonstrated better survival of mice treated with CSL111 (Tanaka et al. 2020). The better chances of survival from sepsis by patients carrying low CETP activity alleles suggest CETP inhibitors as interesting drugs for the treatment of patients with sepsis (Trinder et al. 2019, 2021). However, an important caveat comes from the ILLUMINATE study where torcetrapib treatment was associated with excess mortality due to infections (Barter et al. 2007b).

Although the association of HDL-C with the incidence of viral infections was not statistically significant in the Copenhagen General Population Study (Madsen et al. 2018), it is noteworthy that at least in vitro HDL or apoA-I interferes with the entry or fusion of viruses with target cells (Meilhac et al. 2020; Pirillo et al. 2015). HDLs also induce viral inactivation by immune cells and protect cells from virus-induced damage (Pirillo et al. 2015). The COVID19 pandemia also raised the question of whether HDL interferes with SARS-CoV2 infections. In the UK Biobank study, a linear inverse and independent association was found between pre-infection HDL-C levels and the risk of hospitalization for severe COVID19 (Hilser et al. 2021; Lassale et al. 2021). Mendelian Randomization rather excluded any causal role of HDL in preventing SARS-CoV2 infection. (Hilser et al. 2021). Nevertheless, since SR-BI is an entry route of several viruses including SARS-CoV2 into cells (Pirillo et al. 2015; Wei et al. 2020), competition of this interaction by HDL is an intriguing hypothesis. In addition, the protective effects of HDL on the survival and function of cells may also help infected cells, for example of the lung epithelium or the endothelium (Robert et al. 2021), to combat and survive the entered viruses. Interestingly, dalcetrapib is currently tested towards its effect on the course of COVID19 infections. (Talasaz et al. 2021; https://clinicaltrials.gov/ct2/show/NCT04676867).

Finally, HDL also exerts protective activities towards infections with protozoa. The best example is the protection of humans from Trypanosoma brucei by apoL1 transported by a subfraction of HDL containing also haptoglobin related protein. This complex kills Trypanosome brucei by causing lysosomal swelling (Friedman and Pollak 2020). A similar HDL-related mechanism appears operative towards Leishmania (Samanovic et al. 2009).

3.3.4 Autoimmune Diseases

In an analysis of more than 110,000 participants of The Copenhagen General Population and the Copenhagen City Heart Study, low HDL-C concentrations were associated with elevated risk of developing the composite end point of 42 different autoimmune diseases (Madsen et al. 2019). Among them, the associations of celiac disease, idiopathic thrombocytopenic purpura, Sjögren's disease, diabetes type 1, inflammatory bowel diseases, and Graves' disease showed the strongest and individually significant associations with HDL-C. Currently, no data are available to prove or disprove causality of these associations (Madsen et al. 2021). Neither are the mechanisms understood. They may involve immunomodulatory effects of HDL which are relevant in the development of auto-immunity (Catapano et al. 2014; Pirillo et al. 2015; Rohatgi et al. 2021; Trakaki and Marsche 2021) or protective effects of HDL towards organs attacked by the immune system so that the onset of organ damage or failure and thereby the clinical diagnosis of manifest disease is delayed. For example, the anti-apoptotic effects of HDL on pancreatic beta cells may delay the loss of insulin production in the course of progressing type 1 diabetes (von Eckardstein and Widmann 2014; Yalcinkaya et al. 2020). For inflammatory bowel diseases, preclinical models generated evidence for the therapeutic potential of HDL: Intestinal inflammation was increased in Apoa1 knock-out mice but decreased in mice which overexpressed human APOA1 or were fed with

apoA-I mimetic peptides (Gerster et al. 2014; Meriwether et al. 2019; Nowacki et al. 2016).

3.3.5 Cancer

Several epidemiological studies found inverse associations between HDL-C and cancer in general as well as specific cancers such as breast cancer or colorectal cancer (Ganjali et al. 2021; Madsen et al. 2021; Pirro et al. 2018). Currently, there is no evidence of causality. However, several confounders of low HDL-C are associated with increased risk of several cancers, for example smoking, overweight and obesity, type 2 diabetes, or chronic inflammatory diseases. There is hence some likelihood that low HDL-C is a confounder of other causal risk factors rather than reflecting loss of anti-cancer functions. Even if HDL is not causally related to cancer, it will offer opportunities for therapeutic or diagnostic exploitation: probably to satisfy their high need of cholesterol for growth, many cancers show a high expression of lipoprotein receptors including SR-BI (Hoekstra and Sorci-Thomas 2017; Kinslechner et al. 2018; Velagapudi et al. 2018). This can be exploited by using rHDL for the delivery of anti-cancer drugs or tracers for imaging. In fact, according experiments in preclinical models showed promising results (Morin et al. 2018; Rajora and Zheng 2016).

3.3.6 Behind the Blood Brain Barrier: Alzheimer's Disease and Age Related Macular Degeneration

Until recently, only cross-sectional studies and smaller prospective cohort studies described associations of HDL-C with neurodegenerative diseases including Alzheimer's disease (AD) and age related macular degeneration (AMD). They reported discrepant associations ranging from inverse over none to positive (Kjeldsen et al. 2021a). The situation became clearer but also surprising by recent reports of analyses in the Copenhagen General Population and Copenhagen City Heart Studies. High HDL-C levels >95th percentiles increase the risk of dementia and AD (Kjeldsen et al. 2021b). This association became even more prominent after adjustment for APOE genotypes. Also the risk of AMD was found to increase with HDL-C and even more so with apoA-I levels (Nordestgaard et al. 2021) confirming data on more than 30,000 individuals from the EYE-RISK and European Eye Epidemiology Consortia (Colijn et al. 2019). Of note, in that study higher HDL-C was most strongly associated with increased risk of early AMD. Mendelian Randomization studies found evidence for genetic causality of higher HDL-C for the higher risk of AMD but not AD (Burgess and Smith 2017; Chen et al. 2010; Fan et al. 2017; Neale et al. 2010; Ostergaard et al. 2015; Proitsi et al. 2014), the latter perhaps because of the non-linear relationship. CETP, APOE, and LIPC were important drivers of the genetic association between HDL-C and AMD (Colijn et al. 2019; Chen et al. 2010; Neale et al. 2010). However, candidate gene approaches as well as genome-wide association studies found ABCA1 as a genetic determinant of both AD and AMD risks (Bellenguez et al. 2020; Nordestgaard et al. 2015; Fritsche et al. 2016). Likewise, tissue specific knock-out experiments in mice indicate that loss of ABCA1 function in neurons and retinal pigment epithelial cells

compromise neurocognitive and retinal functions, respectively (Behl et al. 2021; Storti et al. 2019). These discrepant associations of AD and AMD with high HDL-C levels in peripheral blood but locally reduced cholesterol efflux in the brain and retina probably reflect the tight separation of these compartments by the blood brain barrier. Some HDL functions in the brain are executed by HDL-like particles that contain apoE instead of apoA-I and that are produced by astrocytes within the central nervous system (Button et al. 2019). Especially the association of APOE genotypes with risk of AD, although mechanistically not resolved, has been traditionally ascribed to apoE endogenously produced by the CNS rather than supplied by the systemic circulation. Of note however, also the concentration of apoE in plasma of peripheral blood has been associated with risk of AD (Rasmussen et al. 2018). Moreover, anti-apoA-I immunoreactivity is found in the brain. These findings indicate a limiting role of the blood brain barrier for any protective role of HDL in CNS diseases such as AD and AMD. Any therapeutic exploitation of HDL for CNS diseases will have to address the interaction of HDL with the blood brain barrier, either as a target of HDL's protective actions, for example in amyloid beta clearance, or as a barrier that must be surmounted by HDL to exert protective functions within the CNS (Button et al. 2019; Robert et al. 2021). The latter is also important for the use of HDL-like nanoparticles that are currently investigated as vehicles for drug delivery into the brain (D'Arrigo 2020; Kadiyala et al. 2019; Kim et al. 2020).

3.4 Implications for Nowaday's Clinical Practice

As the result of the futile intervention trials, HDL-C unlike LDL-C has not become any treatment goal (Grundy et al. 2019; Mach et al. 2020). However, HDL-C continues to be part of ASCVD risk assessment, both directly and indirectly by using HDL-C for the calculation of nonHDL cholesterol or even LDL cholesterol (Grundy et al. 2019; Mach et al. 2020; Martin et al. 2013; Sampson et al. 2020). Especially in asymptomatic patients without any lipid modifying treatment, a low HDL-C level is considered as a risk factor of developing ASCVD. As such, HDL-C is a component of most clinical risk prediction rules that are promoted by guidelines for the prevention of ASCVD (Grundy et al. 2019; Mach et al. 2020). Unfortunately, these algorithms do not realize the discontinuous relationship of HDL-C with risk, but still de-escalate risk estimates in individuals with very high HDL-C levels. This may be a reason why, for example, in the Copenhagen City Heart study the inclusion of HDL-C impaired rather than improved the prognostic performance of SCORE promoted by ESC and EAS (Mortensen et al. 2015). With the same reasoning, clinical laboratories as well as clinicians and practitioners should stop the still widely spread clinical practice to calculate total cholesterol/HDL-C- or LDL-C/HDL-C ratios because they may underestimate the risk of individuals with high HDL-C (de Wolf et al. 2020; Nordestgaard et al. 2020). The same concern may relate to the atherogenic index – the logarithmically transformed ratio of the molar concentrations of plasma triglycerides to HDL-C – especially because some studies found the joint presence of high HDL-C and hypertriglyceridemia associated with

increased ASCVD risk (Jeppesen et al. 1998; von Eckardstein et al. 1999). Finally, low HDL-C continues to be a component of definitions for the metabolic syndrome, which indicates increased risks not only for ASCVD but also for diabetes and other obesity related diseases (Alberti et al. 2009).

Whether reflecting compromised anti-atherogenic functions or indicating indirectly a proatherogenic situation, the finding of low HDL-C levels should prompt physicians and patients to optimize the control of other risk factors (März et al. 2017). The lost association of low HDL-C with increased risk upon intensive statin therapy indicates the importance of consequent LDL-C lowering in these patients. Additional important measures include cessation of smoking, correction of obesity and overweight, and treatment of hypertension. In view of the inconsistent outcomes of according randomized controlled trials it is a matter of uncertainty and controversy whether or not hypertriglyceridemia which frequently confounds low HDL-C should be targeted by drug treatment (Ginsberg et al. 2021).

The discussion on therapeutic consequences of high HDL-C levels is in its infancy. It is not clear whether the associations of high HDL-C with increased mortality and risks of CKD, infectious diseases, AD, or AMD are causal. An important potential confounder is excess alcohol consumption (Madsen et al. 2021). Potential candidates for HDL-C lowering drugs are probucol, ANGPTL3 inhibitors, or androgens. In the absence of HDL-C lowering treatments with proven efficacy, it is advisable to focus on risk factor control also in patients with high HDL-C as described for patients with low HDL-C.

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